From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/004073	10.12.2004	10.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/165, C07K16/10, C12N15/50, G01N33/68, A61K39/215, A61P31/14

Applicant
AGENCY FOR SCIENCE TECHNOLOGY AND RESEARCH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Fuhr, C Telephone No. +31 70 340-3510

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14,15,44

because:

☒ the said international application, or the said claims Nos. 14,15,44 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,7-20,25,30-36,41-48
	No:	Claims	1-3,5-6,21-24,26-29,37-40
Inventive step (IS)	Yes:	Claims	4,11-17,19-20,32-36,42-48
	No:	Claims	1-3,5-10,18,21-31,37-41
Industrial applicability (IA)	Yes:	Claims	1-13,16-43,45-48
	No:	Claims	14,15,44

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 **Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 Claims 14-15 and 44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2 **Re Item V**

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DATABASE EMBL [Online] 23 April 2003 (2003-04-23), "SARS coronavirus Urbani, complete genome." XP002335172 retrieved from EBI accession no. EM_PRO:AY278741 Database accession no. AY278741

D2: KROKHIN OLEG ET AL: "Mass Spectrometric Characterization of Proteins from the SARS Virus: A Preliminary Report." MOLECULAR & CELLULAR PROTEOMICS : MCP. MAY 2003, vol. 2, no. 5, May 2003 (2003-05), pages 346-356, XP002335128 ISSN: 1535-9476

2.1 Industrial applicability

2.1.1 For the assessment of the present claims 14,15 and 44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.1.2 The subject matter of claims 14, 15 and 44 was assessed for novelty and inventive step as if the wording of said claims was conform to the requirements of Articles 54(2) and 54(4) EPC and paragraph C-IV 4.2 of the EPC guidelines regarding the first or second medical application.

2.1.3 The subject matter of claims 1-13, 16-43 and 45-48 is industrially applicable.

2.2 Novelty

2.2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,3,5,6 is not novel in the sense of Article 33(2) PCT.

2.2.2 D1 disloses the surface spike protein of SARS CoV urbani strain which is coded by codon numbers 21492-25259 of the virus genome (page 6). This spike protein certainly comprises and encompasses neutralizing domains, the heptad region or the peptide fragments having SEQ ID NO. 4. and 5.

2.2.3 In the light of D1, claims 1-3 and 5-6 are not novel (Article 33(2) PCT).

2.2.4 The subject matter of claim 4, and 7-20 is considered to be novel (Article 33(2) PCT).

2.2.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 21-24, 26-29 and 37-40 is not novel in the sense of Article 33(2) PCT.

2.2.6 D2 discloses native, mature and glycosylated spike protein of SARS CoV, isolated from virus culture in Vero E6 cells, having an apparent mass ~180 kDa (page 347, left column, second paragraph - right column, first paragraph). It further discloses that covalescent plasma from a SARS patient was used to identify gradient fractions containing spike protein (page 347, left column, last paragraph). In the light of D2, claims 21-24, 26-29 and 37-40 are not novel (Article 33(2) PCT).

2.2.7 The subject matter of claims 25 and 30-36, 41-48 is considered to be novel (Article 33(2) PCT).

2.3 Inventive Step

2.3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 7-10 and 18 is not inventive in the sense of Article 33(3) PCT.

2.3.2 D1 is considered to be the closest prior art for the subject matter of claims 4 and 8-20. It discloses the (sequence of the) spike protein of SARS CoV.

2.3.3 The difference between the subject matter of claims 4 and 8-20 and D1 are the specific fragments (of claim 4) of the spike protein, methods for production of spike protein fragments, antibodies specific for spike protein or its fragments, and methods, kits and vaccines relating to spike protein and its fragments..

2.3.4 The problem to be solved by present claims 4 and 8-20 can therefore be formulated to be the provision of spike protein or its fragment having a neutralizing domain, antibodies specific therefore and methods, kits and vaccines relating to them.

2.3.5 Claim 7 is not inventive, because it is directed to a method of production of spike protein and its fragments, by employing a standard technique devoid of any surprising or novel features employed to a known protein (Article 33(3) PCT). It is furthermore questionable if all fragments, encompassed by said claim 7 have the alleged activity and solve the technical problem posed.

2.3.6 Claims 8-10 and 18 are not inventive, because it is directed to antibodies specific for a known protein, devoid of any surprising or novel features (Article 33(3) PCT).

2.3.7 The subject matter of claims 4, 11-17 and 19-20 is considered to be inventive, because it is neither obvious nor suggested in the prior art (Article 33(3) PCT).

2.3.8 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 25, 30-31 and 41 is not inventive in the sense of Article 33(3) PCT.

2.3.9 D2 is considered to be the closest prior art for the subject matter of claims 25, 30-36 and 41-48. It discloses glycosylated spike protein isolated from virus culture in Vero E6 cells and its antibody-identification using convalescent serum.

2.3.10 The difference between the subject matter of claims 25, 30-36 and 41-48 and

D2 is the choice of a certain virus strain (2774), the cell type, wherein the spike protein is produced (human lung cells or cos-7 cells) and the method of screening for virus using Endo-H immunoprecipitation and method of detection of SARS infection using spike protein specific antibody and the kit containing said antibody, and vaccines containing the glycosylated spike protein or the spike protein specific antibody.

2.3.11 The problem to be solved by the present application can therefore by found in the provision of spike protein of an alternative strain, the production thereof in an alternative type of cell, the screening and detection methods and the kits and vaccines comprising glycosylated spike protein or its antibody. The problem is solved by present application.

2.3.12 This solution however cannot be considered to be inventive in the case of choice of an alternative virus strain and/or for an alternative (mammalian) cell for protein production, because no special technical effect is disclosed and the skilled person could choose and find such an alternative. Claims 25, 30, 31, 41 thus lack an inventive step (Article 33(3) PCT).

2.3.13 Claims 32-36 and 42-48 do involve an inventive step because their subject matter is not obvious over D2 (Article 33(3) PCT).

3 Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004111081	23.12.2004	14.06.2004	13.06.2003
WO2004092360	28.10.2004	09.04.2004	10.04.2003
WO2005016247	24.02.2005	24.06.2004	24.06.2003

3.1 The above mentioned documents could become relevant for the assessment of novelty and inventive step under Article 54(3) EPC when entering the European phase of the present application.

4 **Re Item VIII**

Certain observations on the international application

4.1 The subject matter of claim 1 is directed to a peptide or protein of SEQ ID NO 1. SEQ ID NO 1 however is a DNA sequence. This inconsistency renders said claim 1 unclear (Article 6 PCT).

4.2 Page 45 of the description has as last paragraph a citation number 16. Page 46 of description has a citation of number 39. It seems that the description was filed incompletely (Article 5 PCT).

4.3 The term 'glycol protein' is not well recognised in the art and appears to have no defined meaning. Since the scope of the claim is to be interpreted in the light of the description, the use of this term renders the scope of the claims unclear (Article 6 PCT).

4.4 It has to be noted that a problem of lack of unity could arise if and when the present application enters the European phase.